POSTER 3: A novel transgenic model to study the stem cells that persist upon tyrosine kinase inhibitor treatment of chronic myeloid leukemia

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Chronic myeloid leukemia (CML) is a myeloproliferative disease driven by BCR-ABLJ, a fusion oncogene that encodes a constitutively active tyrosine kinase. CML is thought to arise when a hematopoietic stem cell (HSC) acquires BCR-ABLJ, leading to transformation and the development ofleukemia. The discovery of tyrosine kinase inhibitors (TKis) that block BCR-ABLl activity has improved CML outcomes. However, lifelong treatment is required as TKI cessation leads to relapse in >50% of patients. Relapse has been attributed to a population of leukemic stem cells (LSCs) that persists despite the presence of TKis and give rise to disease when left unchecked. However, the study of such LSCs has been hindered by the Jack of models that recapitulate the human pathology, notably the chronic phase of CML. We believe that the differences from the human pathology are primarily due to non-specific expression of BCR-ABLJ outside of the pool ofHSCs. To this end, we recently established a novel CML model that enables the inducible expression of a BCR-ABLJ transgene specifically within a fraction of HSCs. Importantly, this transgenic reporter system permits the identification and distinction between normal HSCs and cells that express BCR-ABLJ through differential expression of fluorescent reporters. We investigated long-term impact of BCR-ABLJ expression through continuous analysis of BCR-ABLJ-expressing animais. We found that the absolute numbers of platelets and white blood cells gradually increased in mice expressing BCR-ABLJ compared to contrais. Flow cytometric analyses of hematopoietic stem and progenitor cells (HSPCs) as well as lineage-restricted and mature cell populations showed a rapid expansion of leukemic cells in HSPCs followed by an increase in leukemic myeloid cells in the peripheral blood. The increase in leukemic cells detected in each population occurred at the expense of its normal hematopoietic counterpart. While this expansion of leukemic ce lis occurred within the first 100 days following induction ofBCR-ABLl expression, the survival ofthese mice was prolonged for 3-4 times (average ~250 days) compared to that of other in vivo CML models (60-70 days). Pilot studies of TKI treatment of our CML animais showed a reversal of some effects and restoration of the stem cell compartment suggesting that our model can be used to isolate and study LSCs.